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## Advanced Model Compounds for Understanding Acid-Catalyzed Lignin Depolymerization: Identification of Renewable Aromatics and a Lignin-Derived Solvent

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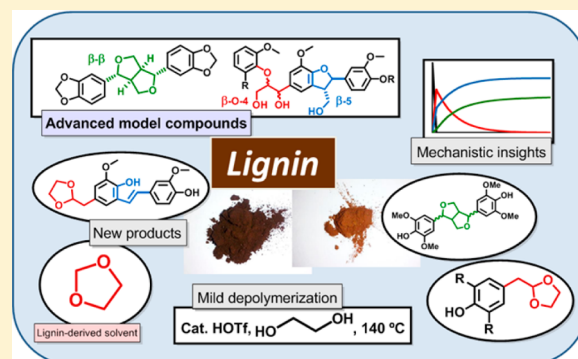
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### Supporting Information

**ABSTRACT:** The development of fundamentally new approaches for lignin depolymerization is challenged by the complexity of this aromatic biopolymer. While overly simplified model compounds often lack relevance to the chemistry of lignin, the direct use of lignin streams poses significant analytical challenges to methodology development. Ideally, new methods should be tested on model compounds that are complex enough to mirror the structural diversity in lignin but still of sufficiently low molecular weight to enable facile analysis. In this contribution, we present a new class of advanced ( $\beta$ -O-4)-( $\beta$ -5) dilinkage models that are highly realistic representations of a lignin fragment. Together with selected  $\beta$ -O-4,  $\beta$ -5, and  $\beta$ - $\beta$  structures, these compounds provide a detailed understanding of the reactivity of various types of lignin linkages in acid catalysis in conjunction with stabilization of reactive intermediates using ethylene glycol. The use of these new models has allowed for identification of novel reaction pathways and intermediates and led to the characterization of new dimeric products in subsequent lignin depolymerization studies. The excellent correlation between model and lignin experiments highlights the relevance of this new class of model compounds for broader use in catalysis studies. Only by understanding the reactivity of the linkages in lignin at this level of detail can fully optimized lignin depolymerization strategies be developed.



### INTRODUCTION

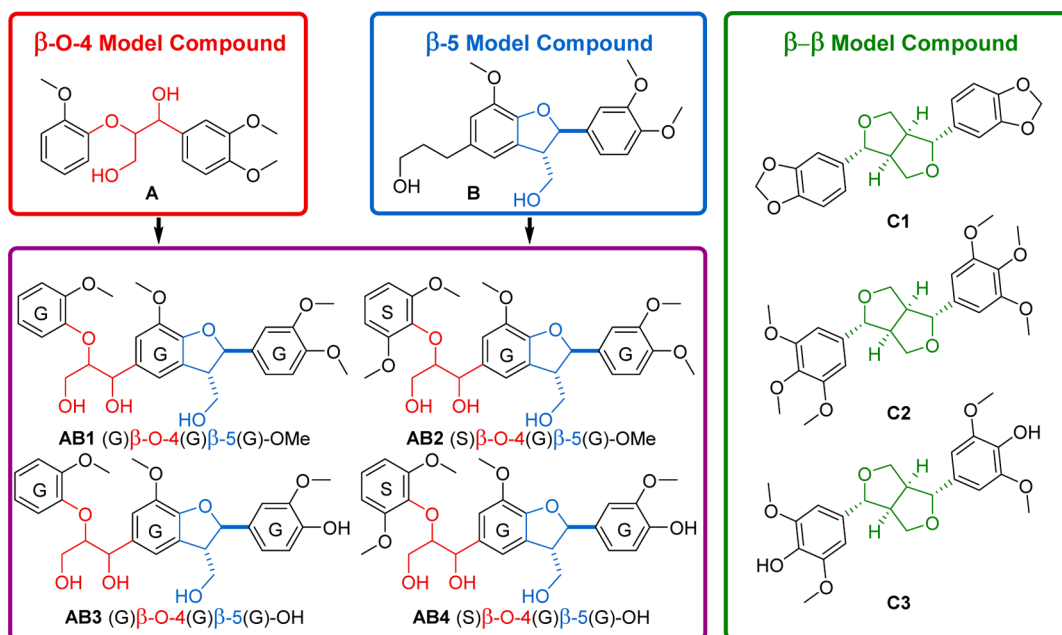
The efficient depolymerization of lignin is one of the major challenges in the full valorization of renewable lignocellulose resources<sup>1,2</sup> and requires fundamentally new catalytic methods.<sup>3,4</sup> However, the development of new approaches is particularly challenging due to the complexity of this aromatic polymer.<sup>2a,5</sup> Methodology development is often done on overly simplified model compounds.<sup>6</sup> In contrast, the work with real lignin streams directly is tedious and leads to extensive analytical challenges including the structural determination of the starting material and the characterization of complex product mixtures.<sup>2a,3a,7</sup> Therefore, the synthesis of new, more advanced model compounds is highly desired and of general importance in this field. Lignin contains different aromatic subunits (H, G, and S) and various types of linkages (Figure S1).<sup>2a,3a,5</sup> The occurrence of these linkages varies greatly depending on the plant type and pretreatment methods used. Thus, far, most studies have focused on the cleavage of the most abundant  $\beta$ -O-4 linkage using predominantly simple model compounds.<sup>2a,3,6,8</sup> Much less effort has

been devoted to understanding the chemistry of other types of linkages such as  $\beta$ - $\beta$ <sup>9</sup> and  $\beta$ -5<sup>10</sup> (Figure S2).<sup>11</sup>

It has become increasingly important to develop more sophisticated model compounds<sup>12,13</sup> that reflect the complexity of the native lignin structure. To the best of our knowledge, synthetic pathways to model compounds that combine multiple linkage types, contain all lignin-relevant functional groups, and at the same time are of limited molecular weight have not yet been developed. In this contribution, we provide scalable synthetic paths to access such advanced lignin model compounds and demonstrate their value in understanding the reactivity of the main linkages in real lignin feedstocks under depolymerization conditions.

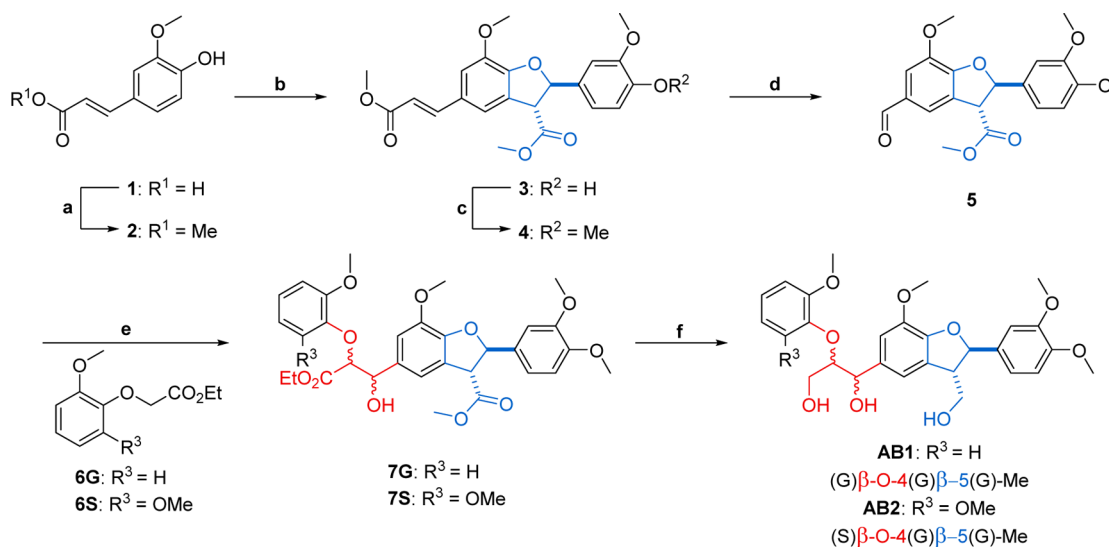
The new class of advanced model compounds (AB1–4) are a combination of the  $\beta$ -O-4 and the  $\beta$ -5 linkage and contain phenolic and nonphenolic units (Figure 1). Variations on the

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**Figure 1.** A summary of model compounds A, B, C1–3 used during our catalytic studies, including novel  $\beta$ -O-4- $\beta$ -5 dilinkage model compounds (AB1–4) synthesized in this work.

**Scheme 1.** Synthesis of Models AB1 and 2<sup>a</sup>



<sup>a</sup>Reagents and conditions: (a) TMSCl, MeOH, reflux, 1 h, 100%. (b) Ag<sub>2</sub>O, DCM, 24 h, 39%. (c) MeI, K<sub>2</sub>CO<sub>3</sub>, acetone, reflux, 5 h, 66%. (d) RuCl<sub>3</sub> (0.1 mol %), NaIO<sub>4</sub>, H<sub>2</sub>SO<sub>4</sub>, EtOAc/MeCN/H<sub>2</sub>O (5:5:2), 0 °C, 3 h, 90%. (e) LDA, THF, −78 °C, 6 h, 82%\* for 7G, 80%\* for 7S. (f) NaBH<sub>4</sub>, MeOH, EtOH, 50 °C, 5 h, 90%\* for AB1, 96%\* for AB2 (\*combined yield of diastereomers).

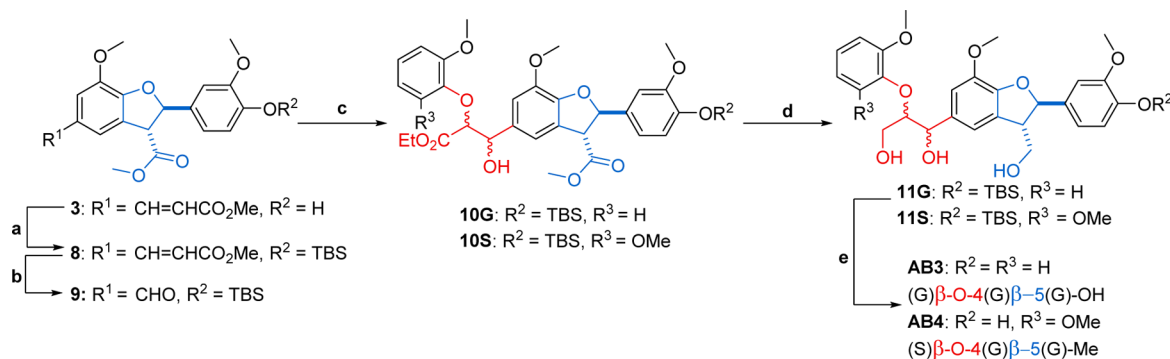
65  $\beta$ -O-4 side include guaiacyl (AB1 and AB3) and syringyl (AB2  
66 and AB4) end groups. The  $\beta$ -5 moiety contains either a non-  
67 phenolic (AB1 and AB2) or phenolic end group (AB3 and AB4),  
68 whereby the methoxy simulates an internal  $\beta$ -5 linkage, whereas  
69 the phenolic group mimics a terminal  $\beta$ -5 linkage or the result of a  
70 cleaved  $\beta$ -O-4 linkage.

71 The reactivity of these model compounds (AB1–4) was sub-  
72 sequently evaluated in a catalytic method we have previously  
73 pioneered, which comprises acidolysis in conjunction with the  
74 stabilization of reactive intermediates under acetal formation  
75 conditions.<sup>14</sup> In addition to AB1–4, model compounds repre-  
76 senting the  $\beta$ - $\beta$  lignin linkage (C1–3) were selected for study.  
77 Furthermore, models A<sup>15</sup> and B<sup>16</sup> were selected for studying

the isolated reactivity of the  $\beta$ -O-4 and  $\beta$ -5 linkages, 78  
79 respectively. Using a combination of these models (Figure 1),  
80 we were able to gain deeper understanding of the overall reac-  
81 tivity of lignin under these conditions. New reaction pathways  
82 and intermediates were established, and important products  
83 have been identified in actual lignin depolymerization mixtures.

## RESULTS AND DISCUSSION

**Synthesis of Novel ( $\beta$ -O-4)-( $\beta$ -5) Lignin Model Com- 85  
pounds.** To access the novel ( $\beta$ -O-4)-( $\beta$ -5) models AB1–4, a 86  
divergent synthetic methodology was developed that allowed 87  
access to both nonphenolic (AB1 and AB2) and phenolic (AB3 88  
and AB4) models (Schemes 1 and 2). Starting from commercially 89

Scheme 2. Synthesis of Phenolic Dilinkage Model Compounds AB3 and AB34<sup>a</sup>

<sup>a</sup>Reagents and conditions: (a) TBSCl, imidazole, DMF, rt, 30 min, 89%. (b) RuCl<sub>3</sub> (0.1 mol %), NaIO<sub>4</sub>, H<sub>2</sub>SO<sub>4</sub>, EtOAc/MeCN/H<sub>2</sub>O (5:5:2), 0 °C, 6 h, 75%. (c) 6G or 6S, LDA, THF, −78 °C, 6 h, 80%\* for 10G and 85%\* for 10S. (d) NaBH<sub>4</sub>, MeOH, EtOH, 50 °C, 5 h. (e) TBAF, THF, 5 min, 80%\* for AB3 and 83%\* for AB4 over 2 steps (\*combined yield of diastereomers).

90 available ferulic acid (1) esterification with MeOH/TMSCl  
91 gave methyl ferulate (2), which when treated with silver(I)  
92 oxide underwent an oxidative dimerization to yield diferulate 3.<sup>17</sup>  
93 This reaction is believed to proceed via a radical mechanism that is  
94 under thermodynamic control yielding the racemic *trans*-diferulate,<sup>18</sup>  
95 which possesses the same stereochemistry as the β-5 units in lig-  
96 nin.<sup>19</sup> Methylation of the phenol in 3 using CH<sub>3</sub>I/K<sub>2</sub>CO<sub>3</sub> gave 4  
97 (Table S1),<sup>20</sup> and subsequent oxidative cleavage of the alkene  
98 in 4 using the RuCl<sub>3</sub>/NaIO<sub>4</sub> system afforded aldehyde 5. The  
99 relative stereochemistry of the β-5 motif in compounds 4 and 5  
100 was confirmed by X-ray crystallography (Supporting Information  
101 section S4.2).

102 The β-O-4 moiety was installed by aldol reaction between  
103 5 and 6G to afford diester 7G in 82% yield. In this unoptimized  
104 aldol protocol, a mixture of both the anti (erythro) and syn (threo)  
105 stereochemistry at the new stereogenic centers was formed in a  
106 3:1 ratio<sup>21</sup> as determined by quantitative <sup>1</sup>H NMR analysis of the  
107 crude reaction mixture (Figure S3). Partial separation of the  
108 isomers could be achieved by column chromatography (Supporting  
109 Information section S4.1). However, in general, isomeric mixtures  
110 at the β-O-4 linkage (A and AB1–4) were prepared and used  
111 throughout this work for two main reasons: (i) In real lignin, the  
112 β-O-4 linkage is known to be present as a mixture of both anti and  
113 syn isomers.<sup>19</sup> (ii) In acid-mediated lignin degradation, the reaction  
114 proceeds via a common intermediate from both the anti or syn  
115 isomer.

116 Diastereomeric mixture 7G was reduced using NaBH<sub>4</sub>/MeOH  
117 in EtOH<sup>22</sup> to give AB1 in 90% yield without separation of the  
118 anti and syn isomers. However, anti and syn diastereomers of  
119 AB1 were obtained on a small scale from the separated isomers  
120 of precursor diester 7G (Supporting Information section S4.1).  
121 Similarly, an aldol reaction between 5 and 6S provided 7S in  
122 80% yield, which upon reduction gave the desired product AB2  
123 as a diastereomeric mixture in 96% yield.

124 To access phenolic model compounds AB3 and AB4, a  
125 protecting group strategy was employed (Scheme 2). Protec-  
126 tion of the phenolic group in 3 with TBSCl/imidazole afforded  
127 TBS-protected 8 in a quantitative yield with no need for further  
128 purification. From 8, following an analogous synthetic route  
129 via 9 and 10G or 10S as outlined previously, TBS-protected  
130 models 11G and 11S were prepared and deprotected (TBAF)  
131 to give phenolic models AB3 and AB4 as mixtures of dia-  
132 stereomers in 80 and 83% yield, respectively, over the final  
133 two steps. With this set of novel models AB1–4 in hand, we

134 decided to study their reactivity in acid-mediated lignin depoly-  
135 merization in the presence of ethylene glycol.

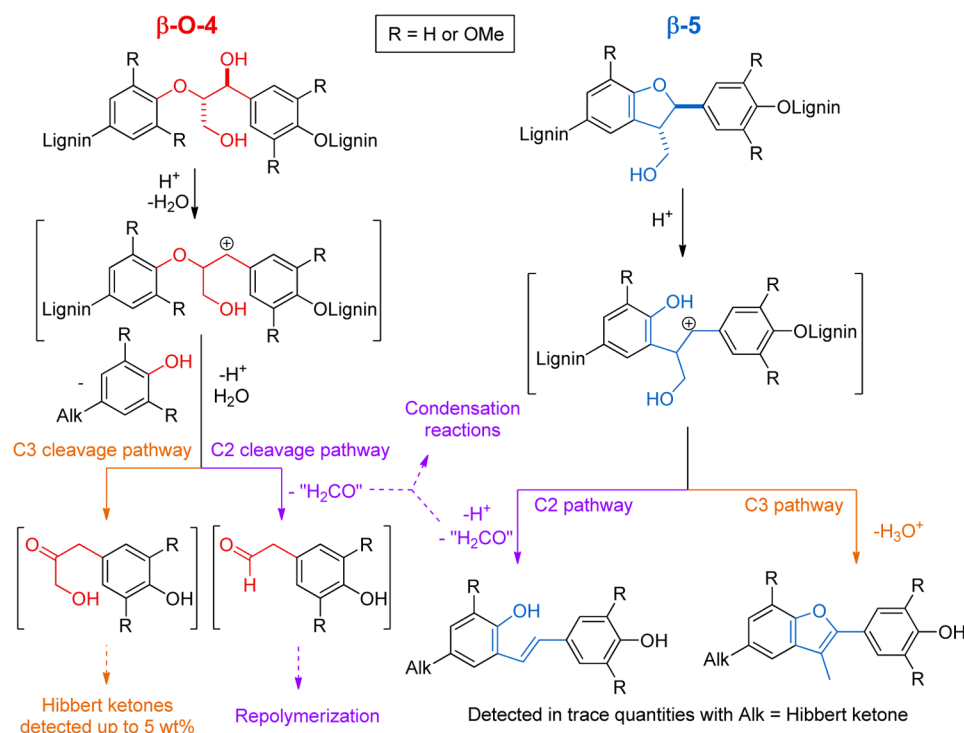
136 **Reactivity of (β-O-4)-(β-5) Model Compounds under**  
137 **Acetal Formation Conditions.** Acidolysis of lignin has  
138 received considerable attention due to the relevance of this  
139 method to the biorefinery concept. This approach was origi-  
140 nally used to aid structural elucidation<sup>11,23</sup> and more recently  
141 for the production of well-defined aromatic compounds.<sup>14,24</sup>  
142 Using model compounds, two different reaction pathways  
143 (C2 and C3 pathways, Scheme 3) have been identified for  
144 the cleavage of the β-O-4 linkage and modification of the β-5  
145 linkage.<sup>24a,b,25</sup> While the C3 pathway provides the Hibbert  
146 ketones, the C2 pathway yields C2-aldehydes upon release  
147 of formaldehyde, which can then undergo condensation reac-  
148 tions.<sup>14,25,26</sup> The balance of these pathways depends on the  
149 nature of the mineral acid used. With HBr, the C3 pathway  
150 dominates, whereas H<sub>2</sub>SO<sub>4</sub> favors the C2 pathway.<sup>26,27</sup> Similar  
151 observations were made regarding the reactivity of the β-5  
152 linkage. Lundquist et al. studied the reactivity of a β-5 model  
153 compound with different acids in mixtures of 1,4-dioxane/H<sub>2</sub>O.  
154 While HBr gave mainly the C3-benzofuran product, triflic acid  
155 (HOTf) gave predominantly the C2-stilbene product.<sup>28</sup>

156 We have previously described the highly efficient cleavage of  
157 β-O-4 lignin model compounds using catalytic amounts of  
158 HOTf in conjunction with *in situ* stabilization of the resulting  
159 C2-aldehyde products as their ethylene glycol acetals.<sup>14</sup> This  
160 concept was also extended to the depolymerization of lignin  
161 where recondensation reactions were markedly suppressed.  
162 However, important questions remained unanswered regarding  
163 the reactivity of the β-β and β-5 lignin linkages, and the  
164 products originating from these moieties were not identified.  
165 Furthermore, the released formaldehyde was neither detected  
166 nor quantified, and its role in recondensation was not clarified.  
167 The models AB1–4 were ideally suited to answer these impor-  
168 tant questions.

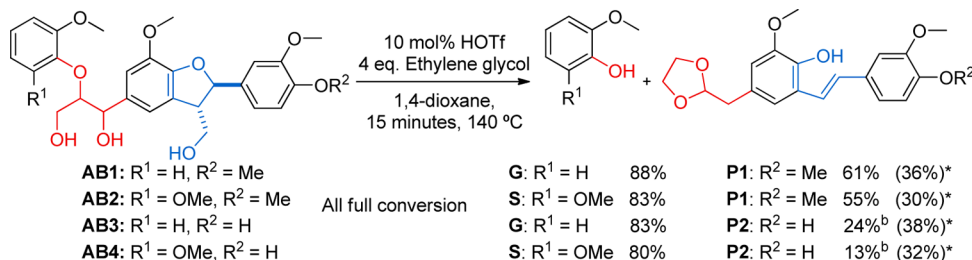
169 **General Reactivity of (β-O-4)-(β-5) Models AB1–4.** First,  
170 the reactivity of AB1–4 was examined under the reaction  
171 conditions we have previously established (HOTf/ethylene  
172 glycol).<sup>14</sup> Full substrate conversion was seen within 15 min,  
173 resulting in the formation of guaiacol G (from AB1 and AB3)  
174 or syringol S (from AB2 and AB4) as determined by HPLC  
175 analysis (Scheme 4). These high yields of G and S were very  
176 similar to those found for simpler β-O-4 model compounds<sup>14</sup>  
177 and demonstrated that the chemistry of the β-O-4 linkage was  
178 unaffected by the presence of the adjacent β-5 moiety.



**Scheme 3. Known Pathways for the Acid-Mediated Cleavage of the Lignin  $\beta$ -O-4 Linkage and the Modification of the Lignin  $\beta$ -5 Linkage (R = H or OMe)**



**Scheme 4. Products Identified in Reactions of the ( $\beta$ -O-4)-( $\beta$ -5) Model Compounds AB1–4<sup>a</sup>**



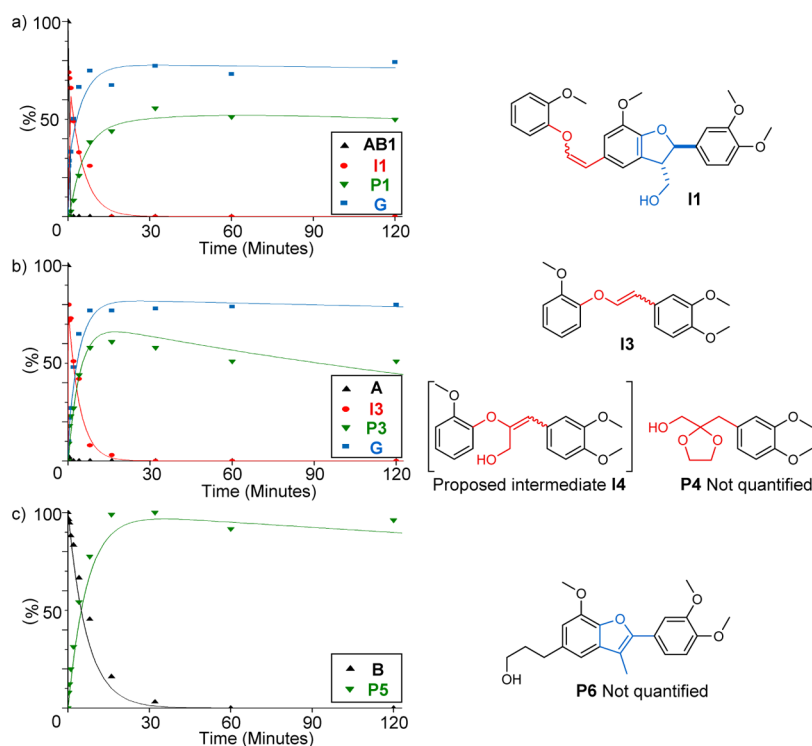
<sup>a</sup>See also Supporting Information sections S6.0 and S9.1. Isolated yields from upscaled procedures with 5 mol % HOTf (Supporting Information section S11.0).

Depending on the substrate used (AB1 and AB2 or AB3 and AB4), novel stilbene-acetals **P1** or **P2** were identified as the other major product (Scheme 4 and Supporting Information section S11.0). These products were likely formed by cleavage of the  $\beta$ -O-4 moiety in AB1–4 to give the C2-aldehyde, which reacted with ethylene glycol (Scheme 3). Subsequent ring opening of the  $\beta$ -5 moiety then occurred also via the C2-pathway.<sup>11b,28</sup> **P1** and **P2** were isolated and fully characterized with the *E* stereochemistry being assigned on the basis of the coupling constants observed between the two alkene protons (16.5 and 16.4 Hz in **P1** and **P2**, respectively; Supporting Information section S11.0).<sup>29</sup>

In control reactions in the absence of ethylene glycol (Supporting Information section S9.2), the  $\beta$ -O-4 linkage was cleaved rapidly, and the guaiacol **G** yields were retained. However, a significant difference was seen in the reactivity of the remaining component of AB1, which formed a mixture of oligomeric products (by GPC analysis, Supporting Information section S7.0). In contrast, GPC analysis of the reaction in the

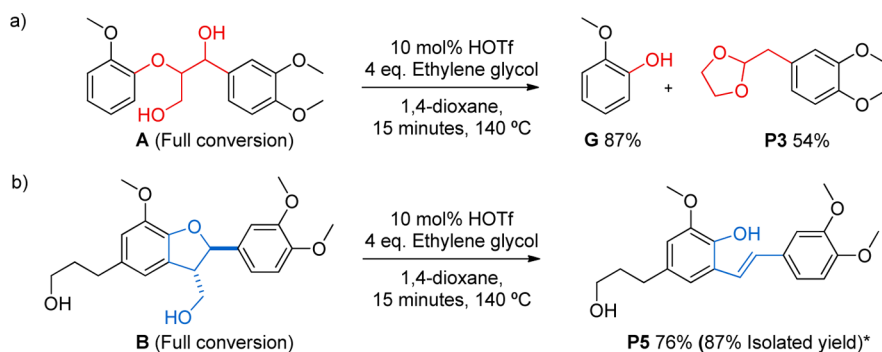
presence of ethylene glycol gave only the desired low molecular weight (LMW) compounds. HPLC analysis also confirmed these observations (Figures S11 and S12) and similar results were obtained from AB3 (Supporting Information sections S7.0 and S9.0).

**Product Formation Profiles and Reaction Intermediates Using ( $\beta$ -O-4)-( $\beta$ -5) Model AB1.** To gain further insight, the acidolysis of AB1 was studied in the presence of ethylene glycol and product formation profiles were recorded (Figure 2a and Supporting Information sections S8.3). While AB1 was consumed within 15 s, guaiacol **G** and acetal-stilbene **P1** were formed at a slower rate, reaching 79 and 56% yields, respectively. Two major signals were also observed by UPLC-MS analysis (both with  $[M + H]^+ = 465 \text{ g mol}^{-1}$ ) prior to the formation of **G** and **P1** (Figure 2a and Supporting Information section S10.1). These were attributed to the formation of isomeric alkenes **I1**, the products of dehydration and deformylation of AB1. While dehydration occurs by loss of the benzylic hydroxyl group in the  $\beta$ -O-4 unit,<sup>25b,26b</sup> deformylation could occur in the  $\beta$ -O-4 unit as well as the  $\beta$ -5 unit in AB1.



**Figure 2.** Reaction profiles using 5 mol % HOTf and 4 equiv of ethylene glycol at 140 °C in 1,4-dioxane with (a) ( $\beta$ -O-4)-( $\beta$ -5) model compound **AB1**, (b)  $\beta$ -O-4 model compound **A**, and (c)  $\beta$ -5 model compound **B**. Dots show experimental data points, whereas the line is a modeled reaction profile (see also [Supporting Information sections S8 and S10](#)).

#### Scheme 5. Reactions with HOTf and Ethylene Glycol with Model Compounds<sup>a</sup>



<sup>a</sup>(a)  $\beta$ -O-4 Model compound **A** and (b)  $\beta$ -5 model compound **B**. Isolated yields from upscaled procedures with 5 mol % HOTf ([Supporting Information section S11.0](#))

Compounds **A**<sup>15</sup> and **B**<sup>16</sup> were used to investigate this issue further.

*Study of the Relative Reactivity of  $\beta$ -O-4 and  $\beta$ -5 Units in **AB1**.* In a reaction with 10 mol % HOTf  $\beta$ -O-4, model **A** yielded 87% **G** and 54% acetal **P3** ([Scheme 5a](#)). Next, the reaction was monitored for 2 h ([Figure 2b](#) and [Supporting Information sections S8.1 and S10.2](#)). This revealed that **A** was rapidly consumed and that two main products were formed ( $[M + H]^+ = 287 \text{ g mol}^{-1}$  by UPLC-MS). This reactivity pattern was analogous to that observed for **AB1**, and the detected mass of the products confirmed the formation of isomeric enol ethers **I3**, formed by acid-catalyzed dehydration/deformylation of the  $\beta$ -O-4 moiety en route to the C2-aldehyde. **I3** was further converted to **G** in 80% yield and **P3** in 61% yield.

When no ethylene glycol was added **G** was still obtained in good yield (69%), but the C2-aldehyde was not observed due

to its conversion to a complex mixture of products, as seen for **AB1** under these conditions ([Supporting Information section S9.0](#)). During these reactions, ketal **P4**, the ethylene glycol ketal of the Hibbert ketone,<sup>25a,30</sup> was also identified (UPLC-MS, [Supporting Information section S10.2](#)). Its formation provided evidence for the functioning of the C3 cleavage pathway in these reactions. This pathway also leads to the formation of guaiacol **G**, so this explains the discrepancies between the yields of **G** and **P3** from **A** (and analogously the differences between the yields of **G** and **P1** formed from **AB1** above). Dehydrated intermediate **I4** ([Figure 2b](#)), the most likely precursor of **P4**, was previously observed when water was used as solvent but could not be detected under our reaction conditions.<sup>24a,b</sup>

Next, the reactivity of the  $\beta$ -5 model **B** was investigated. Upon reaction of **B** with 10 mol % HOTf and 4 equiv of ethylene

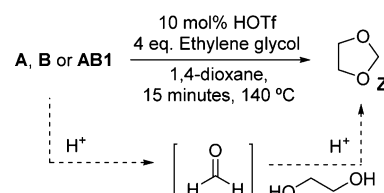
glycol, *E*-stilbene **P5** was obtained in 76% yield (Scheme 5b). However, the consumption of **B** was slow compared to those of **A** and **AB1**, and full conversion of **B** was only achieved after 30 min in contrast to 15 s for **A** and **AB1** (Figure 2c; Supporting Information section S8.2). The rates of formation of **P5** corresponded to the rates of **B** consumption, and no other reaction intermediates were identified. This is consistent with either the concerted deformylation/ring opening of **B** or the formation of short-lived intermediates en route to **P5** ( $\beta$ -5 C2 pathway shown in Scheme 3). Dehydrated benzofuran **P6** (Figure 2c) was identified as minor side product (UPLC-MS, Supporting Information section S10.3). **P6** originates from the C3-pathway previously identified on acid-catalyzed modification of the  $\beta$ -5 linkage (Scheme 3).<sup>28</sup>

**Proposed Reaction Pathways in Acidolysis of AB1.** Returning to the reactivity of **AB1** under acidolysis and acetal forming conditions, a series of reaction pathways were constructed (Scheme 6), and rate analysis provided the curve fits shown in the corresponding figures (on rate modeling, see Supporting Information section S8.0). The **AB1** acidolysis products ( $[M + H]^+ = 465 \text{ g mol}^{-1}$ ) were assigned to the *E* and *Z* isomers of enol ether **I1**, products of the reverse Prins reaction of **AB1** in which the  $\beta$ -5 linkage remains unmodified. This is consistent with the very fast formation of **I3** from **A**. The subsequent cleavage of **I1** to form **G** and an elusive intermediate **I1a** (calculated rate of consumption **I1** =  $0.35 \text{ min}^{-1}$  vs **I3** =  $0.22 \text{ min}^{-1}$ ) is the subsequent step followed by the modification of the  $\beta$ -5 linkage via C2 pathway to give the final acetal stilbene product **P1** (rate of formation =  $0.14 \text{ min}^{-1}$  for both **P1** and **P5**). The C3 pathway for the  $\beta$ -5 modification also occurs as a minor side reaction providing traces of **P8** similar to the traces of **P6** formed from **B**. The second existing route by which **G** is formed from **AB1** is the C3 pathway analogous to that identified using the  $\beta$ -O-4 model compound **A**. This route leads to **P7** ( $[M + H]^+ = 403 \text{ g mol}^{-1}$ ), the corresponding Hibbert ketal analogue (Supporting Information section S10.1). For the  $\beta$ -O-4 cleavage,

the C2 pathway is dominant over the C3 pathway under these reaction conditions (a 3:1 ratio based on the modeled rates and the **P1** to **G** yield discrepancy). The ring opening of the  $\beta$ -5 linkage occurs nearly exclusively via the C2 pathway.

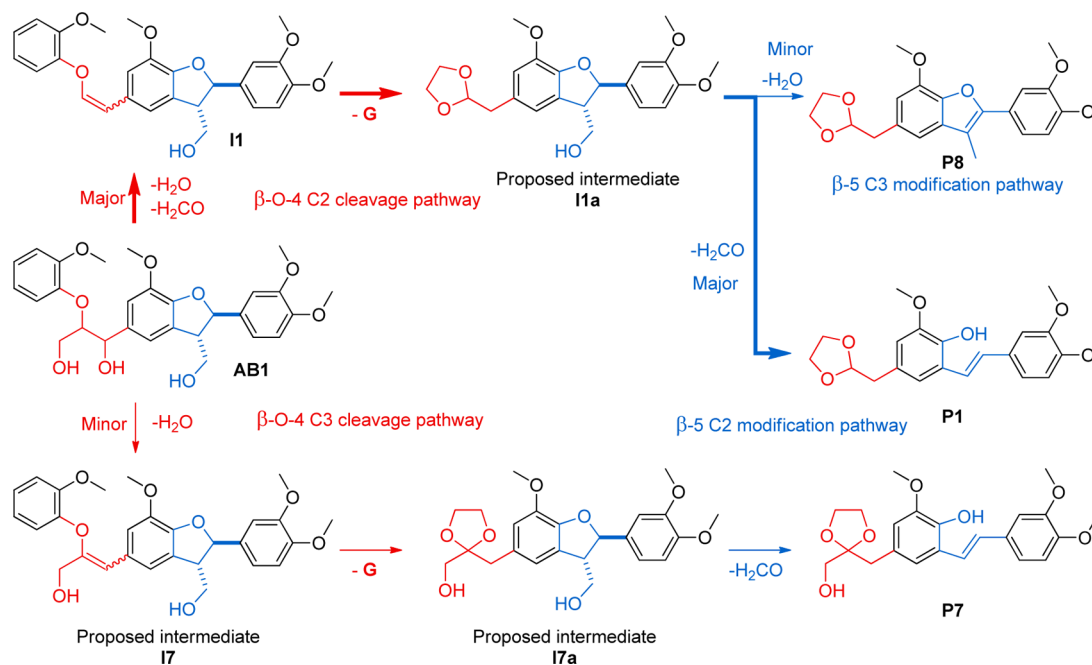
**Determination and Quantification of the Formaldehyde Released from the ( $\beta$ -O-4)-( $\beta$ -5) Models.** During the acidolysis of models **AB1**, **A**, and **B**, the C2 reaction pathways for both the  $\beta$ -5 and  $\beta$ -O-4 linkages involve the formal loss of a carbinol group. Although previous studies agree that this is achieved through the release of formaldehyde,<sup>24b,25</sup> there has been little direct evidence to support this or attempts to quantify the amount of formaldehyde released, likely due to experimental difficulties. Our unique reaction conditions, however, allow for identification and quantification of the released formaldehyde trapped as its ethylene glycol acetal, 1,3-dioxolane **Z** (Scheme 7).

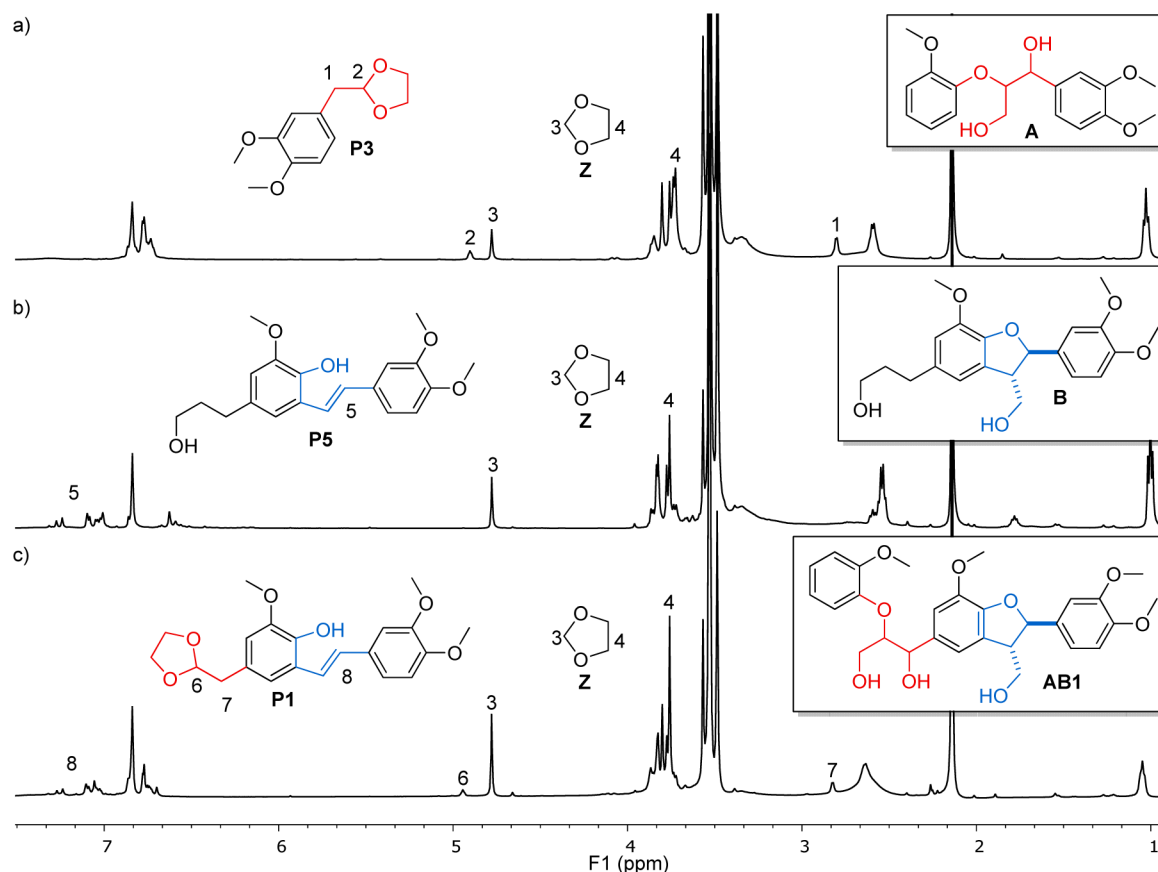
**Scheme 7. 1,3-Dioxolane Z Formation from the Reactions of A, B, or AB1 with HOTf and Ethylene Glycol**



Reactions of **AB1**, **A**, and **B** were repeated in *d*<sub>8</sub>-1,4-dioxane. In all cases, the corresponding 1,3-dioxolane **Z** was clearly identified (signals at  $\delta$  4.77 and  $\delta$  3.76 in <sup>1</sup>H NMR spectra), and the amounts of **Z** as well as acetal products **P1** and **P3** were quantified using an internal standard (Figure 3, for details see Supporting Information section S12). In the case of **A**, a 56% yield of **Z** was observed and this matched well with the 66% yield of C2-acetal **P3** found in the same sample (Figure 3a and Supporting Information section S12.1). Also, for the  $\beta$ -5 model **B**, the amount of **Z** (81% yield) was consistent with that of the

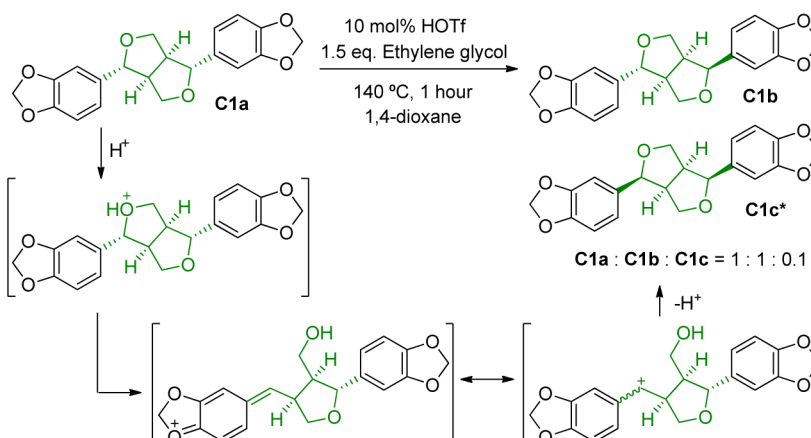
**Scheme 6. Overview of the Detected Reaction Sequences from the HOTf-Catalyzed Cleavage and Modification of AB1 in 1,4-Dioxane at 140 °C**





**Figure 3.** Crude  $^1\text{H}$  NMR spectra of the reactions of (a) **A**, (b) **B**, and (c) **AB1**. Reaction conditions: 10 mol % HOTf, 4 equiv ethylene glycol, 1,4-dioxane- $d_8$ , 140  $^\circ\text{C}$ , 15 min, and 1,2,4,5-tetramethylbenzene as internal standard.

### Scheme 8. Epimerization of $\beta$ - $\beta$ Model C1a under Acid Conditions<sup>a\*</sup>



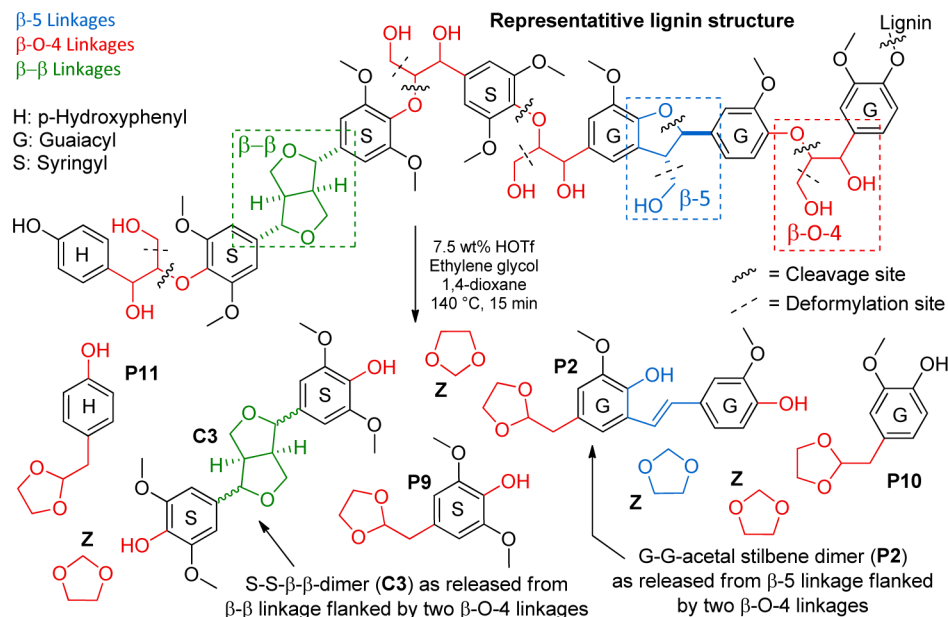
<sup>a\*</sup>: Via a second epimerization reaction at the other benzylic position

corresponding C2 product, **P5** (76% yield by HPLC from a separate reaction, Figure 3b and Supporting Information section S12.2). Finally, for **AB1** an 85% yield of **Z** based on the release of 2 equiv of formaldehyde was found (Figure 3c and Supporting Information section S12.3). The amount of **P1** was slightly lower than expected based on the yield of **Z** (62% **P1** vs 85% **Z**), but is consistent with the HPLC yields discussed above (Scheme 4) combined with the observation that the C3 pathway for the cleavage of the  $\beta$ -O-4 linkage still leads to a product in which the  $\beta$ -5 unit has been modified according to the C2 pathway leading to additional **Z** (Scheme 6). The observed

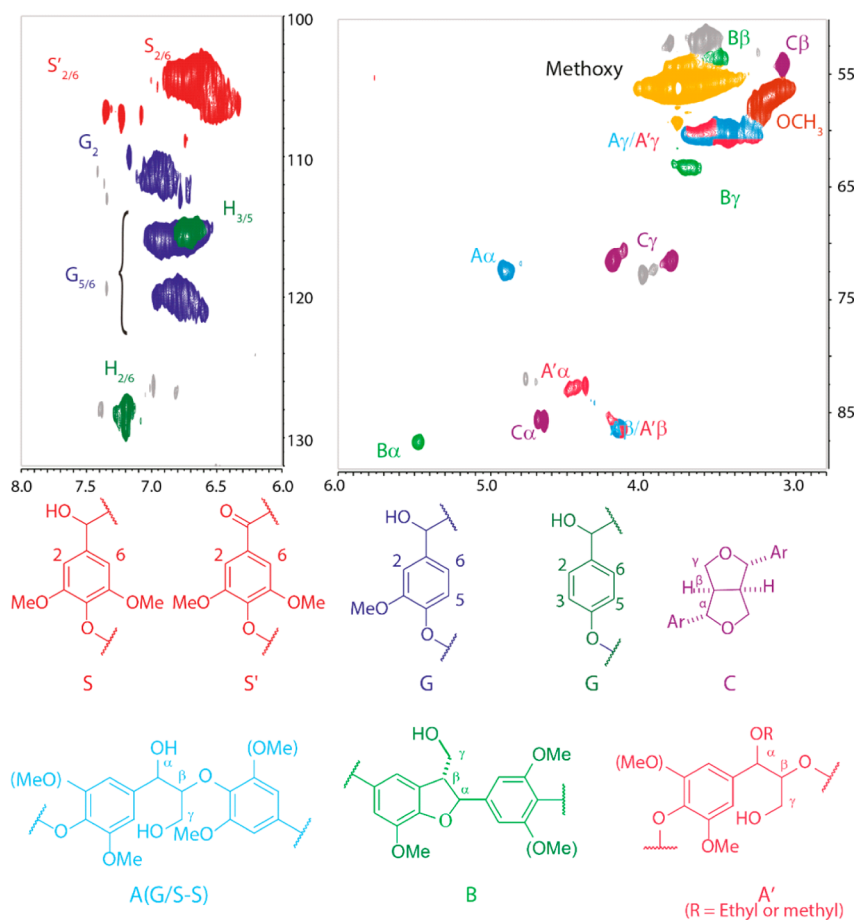
quantities of **Z**, together with the identified products of the complementary C2 pathways, are strong indications that most of the released formaldehyde is trapped as its corresponding acetal. Formaldehyde has been previously implicated in condensation reactions;<sup>14,31</sup> thus, the use of ethylene glycol in our catalytic system contributes to eliminating the adverse effects of formaldehyde. This, together with the trapping of other reactive intermediates (aldehydes), explains the success of this methodology when applied to lignin.<sup>14</sup>

**Examination of the Reactivity of  $\beta$ - $\beta$  Model Compounds.** The effect of our standard acidolysis conditions on



Scheme 9. Schematic Showing of Specific Linkages as They Would Appear in Lignin and Expected Cleavage Products<sup>a</sup>

<sup>a</sup>A hypothetical lignin structure is shown containing  $\beta$ -O-4,  $\beta$ -5 and  $\beta$ - $\beta$  linkages.



**Figure 4.** 2D HSQC NMR spectrum of walnut methanosolv lignin showing areas used for the quantification of visible linkages and determination of S/G/H ratios.

the  $\beta$ - $\beta$  motif was studied using the model **C1a** (sesamin, **Scheme 8**) because **C1a** has the same relative configuration as the  $\beta$ - $\beta$  linkage in lignin.<sup>5,9a</sup> Acidolysis of **C1a** led to a remarkably

clean reaction (**Supporting Information section S13.1**) with the main products being epimers **C1b** (asarinin/episesamin) and **C1c** (epiasarinin/diasesamin, **Scheme 8**).<sup>9b,32</sup> The ratio of **C1a**/**C1b**/**C1c**

was 1:1:0.1 (<sup>1</sup>H NMR, Figure S19) with a >95% mass balance (GC-FID) being observed. Reaction of C1a in the absence of ethylene glycol provided the same product mixture indicating little influence of the diol on this reaction (Figure S20). The same product distribution was also observed when C2a (yangambin) was reacted under these conditions (Figure S21). Epimerization reactions for similar compounds have been previously reported using different Lewis acids.<sup>9a,b,32</sup> Phenolic versions of these compounds (e.g., pinosresinol and syringaresinol C3, Figure 1) and their epimers were previously obtained during lignin acidolysis<sup>11c,23a,26a</sup> and were again identified in this work (*vide infra*). These results indicate no effect of ethylene glycol on the products formed via acidolysis of the  $\beta$ - $\beta$  motif in lignin.

**Identification of Dimeric Products in Lignin-Derived Product Mixtures.** This work culminated in our analysis of lignin-derived product mixtures to assess if the reactions observed in the model compounds translated to the natural material itself. A typical organosolv lignin consists predominantly of the most abundant  $\beta$ -O-4 linkage and the less abundant (about 10%)  $\beta$ -5 and  $\beta$ - $\beta$  linkages (other minor linkages were not considered).<sup>5</sup> Therefore, it is very likely that the  $\beta$ -5 linkages will be flanked by  $\beta$ -O-4 linkages, a situation that inspired the design of AB1–4. The same will hold true for the  $\beta$ - $\beta$  linkages. Exposure of lignin to our catalytic acidolysis conditions would therefore be expected to give phenolic acetals P9–11 as the major products via the C2-pathways because they result from the cleavage of neighboring  $\beta$ -O-4 linkages (Scheme 9)<sup>14</sup> as well as small amounts of Hibbert ketals via the C3 pathway. A  $\beta$ -5 dimer flanked by two  $\beta$ -O-4 linkages should result in stilbene compounds such as P2 via the C2  $\beta$ -O-4 cleavage pathway plus smaller amounts of ketal structures such as P7 (Scheme 6) through the C3  $\beta$ -O-4 cleavage pathway. A  $\beta$ - $\beta$  dimer flanked by two  $\beta$ -O-4 linkages should give epimerized diphenolic  $\beta$ - $\beta$  fragments like C3 (Scheme 9).<sup>11c,23a</sup>

To confirm this, catalytic depolymerization reactions were carried out using pine, beech, and walnut shell organosolv lignins. These lignins were obtained by standard organosolv processing and characterized using 2D HSQC NMR (Figure 4) and GPC for which the most relevant data are summarized in Table 1 (Isolation and characterization details in Supporting Information sections S14.0 and S15.0).

Next, 50 mg samples of these lignins were subjected to the catalytic acidolysis conditions. The crude reaction mixtures were processed by extraction to obtain LMW and high molecular weight fractions (Supporting Information sections S16.0 and S17.0). The LMW fractions were analyzed by GC-FID and GC-MS, and the expected main product acetals (P9–11, Scheme 9) were quantified using an internal standard (Table 2). The P9 versus P10 ratios corresponded well to the amount of S and G

**Table 2. Product Distribution P9–P11 Obtained from Lignin Acidolysis Reaction Using HOTf and in the Presence of Ethylene Glycol<sup>a</sup>**

entry	lignin	P9 (wt %) <sup>b</sup>	P10 (wt %) <sup>b</sup>	P11 (wt %)	total P9–11 (wt %)
1	pine methanosolv		4.4	0.1	4.5
2	beech ethanosolv	4.8	2.6		7.4
3	walnut methanosolv	7.0	3.9	0.4	11.3

<sup>a</sup>Distributions are those shown in Scheme 9. Conditions: 50 mg of lignin, 60 mg of ethylene glycol, 7.5 wt % HOTf, 1 mL of 1,4-dioxane, 30 min, 140 °C, in sealed pressure vessel, *n*-octadecane as GC internal standard. LMW fraction was obtained by extraction of dried reaction solid with 9:1 toluene/DCM. <sup>b</sup>Determined by GC-FID referring to the starting lignin.

units in the lignin starting material. Moreover, the total acetal yields for the respective lignins were dependent on the number of  $\beta$ -O-4 linkages in the original lignin (compare Tables 1 and 2). In the case of ethanosolv beech lignin, the  $\beta$ -O-4 moiety showed increased ethanol incorporation as a result of the organosolv procedure.<sup>33</sup> This is a likely explanation of the slightly higher than expected acetal yields based on the overall  $\beta$ -O-4 content determined by NMR. All acetal yields corresponded well to the isolated yields that we have previously reported (Supporting Information section S17.0 for analysis details).<sup>14</sup> In these reactions, small amounts of products were also seen that correlate to cleavage of the  $\beta$ -O-4 moiety via the C3-pathway, including P12 (Figure 5a).

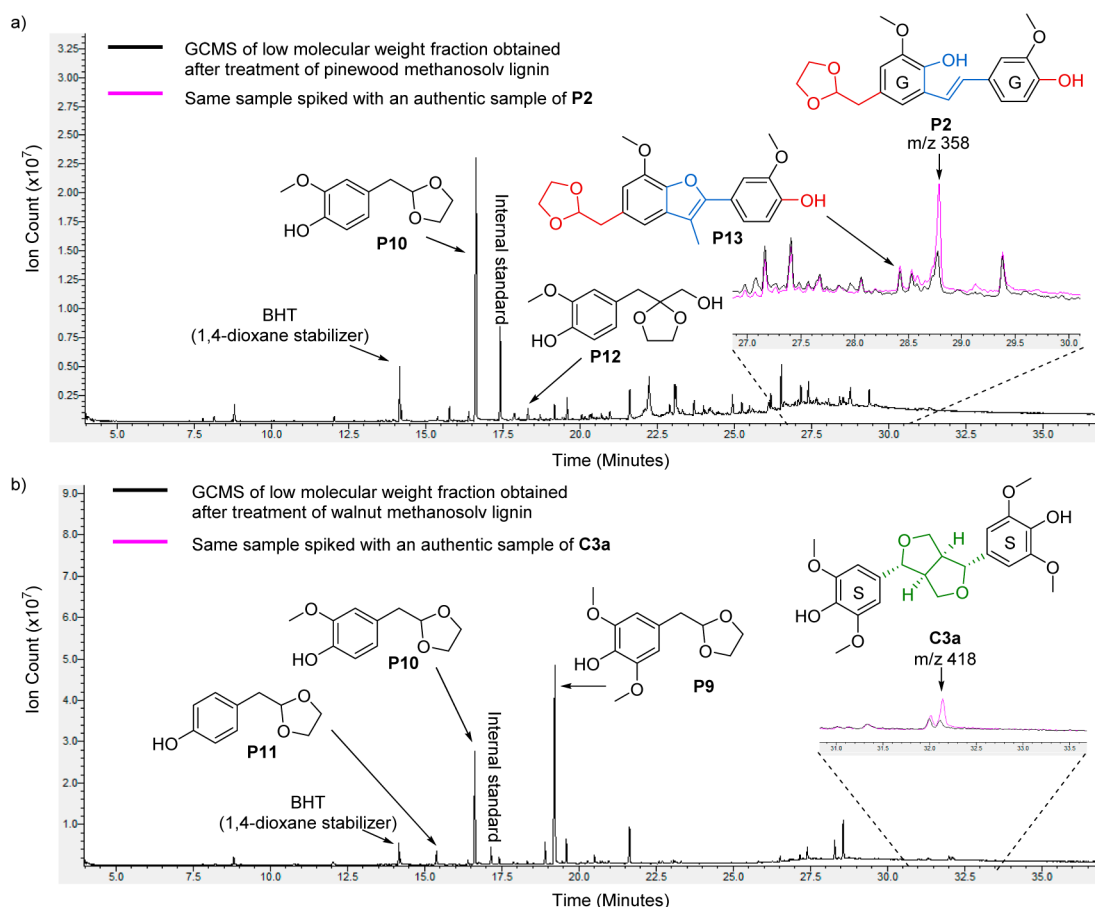
The product mixtures from pine lignin were investigated first. Gratifyingly, acetal stilbene P2 could be identified by GC-MS analysis and its presence verified by spiking with an authentic sample of P2 (Figure 5a and Table S8). The yield of P2 was determined as 2 wt %, in agreement with the relatively high percentage of  $\beta$ -5 linkages (10 per 100 aromatic units) in this lignin. Because pine lignin contains only G units, none of the corresponding S containing acetal stilbenes were observed. Compound P13 (analogous to P8) was also detected (Figure 5a). No  $\beta$ - $\beta$  dimer fragments were identified in this reaction mixture given the limited amount of such linkages present in this lignin (<1  $\beta$ - $\beta$  linkages per 100 aromatic units, Table 1).

The beech organosolv and the walnut shell methanosolv lignins were richer in  $\beta$ - $\beta$  linkages (4 and 8  $\beta$ - $\beta$  linkages per 100 aromatic units respectively); thus,  $\beta$ - $\beta$ -containing fragments derived from these lignins were successfully identified. The presence of syringaresinol C3a was verified by spiking with an authentic sample for both lignins (Figures 5b and S29). C3a and epimer C3b were found as a 1:1 mixture and identified based on their identical molecular weight and fragmentation patterns.

**Table 1. Lignin Characteristics Determined by GPC and 2D-HSQC Analysis**

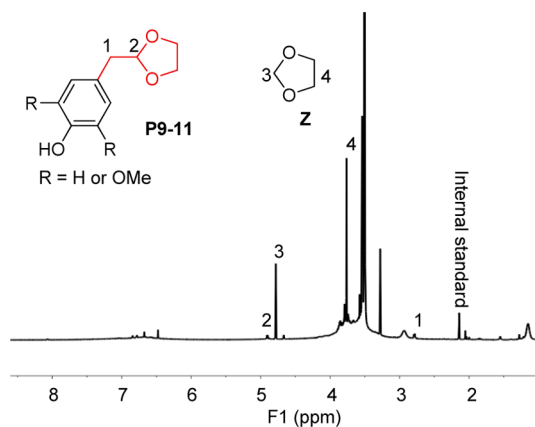
entry	lignin	$M_n$ (Da), $M_w$ (Da), $\bar{D}^a$	S, G, H (%) <sup>b</sup>	linkages (per 100 C <sub>9</sub> units) <sup>c</sup>			
				$\beta$ -O-4 <sup>d</sup>	$\beta$ -O-4-OR <sup>e</sup>	$\beta$ -5	$\beta$ - $\beta$
1	pine methanosolv	1075, 2088, 1.9	0, 100, trace	11	5	10	1
2	beech ethanosolv	928, 2016, 2.2	68, 32, 0	7	4	3	4
3	walnut methanosolv	808, 1518, 2.2	65, 29, 6	26	12	7	8

<sup>a</sup>Determined by GPC (THF) against polystyrene standards (Supporting Information section S15.1). <sup>b</sup>Determined by 2D-HSQC using signal intensities of the corresponding aromatic signals corrected for the amount of protons (Supporting Information section S15.2). <sup>c</sup>Determined by 2D-HSQC by comparing the signal intensities of the aromatic signals to the intensities of the benzylic protons of the linkages corrected for the amount of protons (Supporting Information section S15.2). <sup>d</sup>Total number of  $\beta$ -O-4 linkages. <sup>e</sup>Amount of  $\alpha$ -methoxylated/ethoxylated units.



**Figure 5.** GC-MS traces of product mixtures obtained from the depolymerization of (a) methanosolv pine lignin and the same sample spiked with an authentic sample of compound **P2** and (b) beech wood ethanosolv lignin and the same sample spiked with an authentic sample of compound **C3a**. Reaction conditions: 50 mg of lignin, 60 mg of ethylene glycol, 7.5 wt % HOTf, 1 mL of 1,4-dioxane, 30 min, 140 °C, in sealed pressure vessel, *n*-octadecane as GC internal standard (For more detailed analysis of the GC-MS trace, see [Supporting Information section S17.2](#)).

The observation of **C3**, a  $\beta$ - $\beta$  dimer of two **S** units, is consistent with the relatively high amount of **S** units in these lignins. In addition, it is known that **S** units are more likely to undergo  $\beta$ - $\beta$  dimer formation during lignin biosynthesis.<sup>34</sup> The combined yields of these epimers from beech and walnut lignin were 2.6 and 5.5 wt %, respectively, in line with the amount of the respective linkages in these lignins (GC-MS analysis see [Tables S9 and S10](#)). Additionally, in the samples obtained from the walnut methanosolv lignin, trace quantities of **P2** and **P13** were observed. The above results clearly demonstrate that the chemistry established using ( $\beta$ -O-4)-( $\beta$ -5) model compounds **AB1–4** as well as  $\beta$ - $\beta$  model compounds **C1** and **C2** using acetal formation conditions can be directly extrapolated to the depolymerization of lignin under the same conditions. The unambiguous identification of structurally diverse dimeric compounds such as **P2** or **C3** in complex lignin-derived product mixtures would prove extremely challenging solely based on GC-MS or UPLC-MS analysis. With lignin-relevant model compounds such as **AB1–4**, however, the formation of these compounds can be rationalized. Analysis of the product mixtures also confirmed the dominance of the **C2** reaction pathways, which should coincide with formaldehyde release from the  $\beta$ -O-4 and  $\beta$ -5 motifs. A separate set of experiments was conducted to confirm this using beech ethanosolv and walnut methanosolv lignin in *d*<sub>8</sub>-1,4-dioxane. The <sup>1</sup>H NMR analysis of these reactions revealed the formation of 1,3-dioxolane **Z** (Figure 6 and [Supporting Information section S18.0](#)). The yields of



**Figure 6.** <sup>1</sup>H NMR spectrum of the crude reaction mixture obtained from the depolymerization of 50 mg of walnut methanosolv lignin demonstrating the formation of 1,3-dioxolane **Z**. Reaction conditions: 7.5 wt % HOTf, 60 mg of ethylene glycol at 140 °C for 30 min, quenched by the addition of 5  $\mu$ L Et<sub>3</sub>N.

**Z** from beech and walnut lignin were 1 and 4.2 wt %, respectively (quantified using an internal standard). This corresponds to the amounts of acetals **P9–P11** detected. It is remarkable that the reactivity trends established using our new models **AB1–4** were also in good agreement in terms of formaldehyde release with the results obtained with actual lignin samples.



A further advantage of trapping the released formaldehyde is that it leads to a more complete overall carbon mass balance of the lignin depolymerization reaction. The high yield of 1,3-dioxolane **Z** bodes well for the large-scale production of this compound from lignin, in addition to the valuable aromatics, because 1,3-dioxolane **Z** already finds use as a solvent.

## CONCLUSIONS

We have described the synthesis of a new class of ( $\beta$ -O-4)-( $\beta$ -5) lignin models **AB1–4** that are realistic representations of an abundant lignin fragment (particularly in softwoods). These models allowed for in-depth catalysis studies and enabled a detailed understanding of the controlled catalytic depolymerization of lignin itself. This was possible because **AB1–4** are sufficiently complex to mimic lignin reactivity but still enable product analysis. We also gained detailed insight into the acid-catalyzed cleavage of **AB1–4** as well as other  $\beta$ -O-4,  $\beta$ -5 and  $\beta$ - $\beta$  model compounds. It was demonstrated that the mild depolymerization strategies presented herein were highly efficient in the cleavage of C–O bonds, whereas the main C–C linkages in the  $\beta$ -5 and  $\beta$ - $\beta$  were left intact, with the only C–C bond scission being the release of formaldehyde. Therefore, to obtain high yields of aromatic monomers, lignins with high  $\beta$ -O-4 content are desired. The structure and quantity of dimeric products however relates to the type and number of C–C bonds present in the starting lignin structure. Major reaction pathways (C2 and C3, Schemes 3 and 6) and important intermediates were identified. In addition, novel dimeric products, such as *E*-acetal stilbenes **P1** and **P2** were isolated. This has, for the first time, allowed the identification of these products in depolymerization mixtures generated from pine and walnut lignins.

Recently, Sels and co-workers found the use of ethylene glycol beneficial in reductive lignin depolymerization.<sup>35</sup> Our previous studies also addressed the advantages of using ethylene glycol under acidolysis conditions.<sup>14</sup> Herein, we further specified the benefits of using ethylene glycol in our reactions. First, ethylene glycol stabilizes the various C2-aldehydes formed on cleavage of the  $\beta$ -O-4 linkages. Further, ethylene glycol plays a role in “trapping” the formaldehyde released both from the  $\beta$ -O-4 as well as the  $\beta$ -5 linkage. Importantly, we were able to quantify the amount of released formaldehyde in model and lignin reactions via the corresponding 1,3-dioxolane **Z** formed.

Overall, a close correlation between the reactivity of **AB1–4** and lignin was found. Thus, our novel ( $\beta$ -O-4)-( $\beta$ -5) lignin models should find general use in future catalytic lignin depolymerization studies and will enable further improvements in our understanding of the reactivity of lignin. This is an essential component of establishing financially viable biorefineries.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b04144.

Synthetic procedures and analytical data for described model compounds; procedures and analytical data for reactions with model compounds as well as product isolation and characterization; lignin isolation procedures and characterization; lignin depolymerization procedures; analytical data for product mixtures (PDF)  
Crystallographic data for compounds **4** and **5** (CIF)

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### Notes

The authors declare no competing financial interest.

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